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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/649,413

08/27/2003

Axel Ullrich

224160

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11/17/2008

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EXAMINER

SHAFFER, SHULAMITH H

ART UNIT

PAPER NUMBER

1647

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/649,413	Applicant(s) ULLRICH ET AL.	
	Examiner SHULAMITH H. SHAFER	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 August 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3,4 and 13 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 4, 13 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. ____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

Detailed Action

Status of Application, Amendments, And/Or Claims:

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11 August 2008 has been entered.

The amendment received 9 May 2008 has been entered. Claims 1, and 4 have been amended and the amendments have been entered. Claims 1, 3, 4, and 13 are pending and under consideration.

Withdrawn Rejections

The rejection of Claims 1 and 4, under 35 U.S.C. 112, first paragraph, scope of enablement, is withdrawn in light of applicants' amendment to the claims.

Maintained/New Rejections

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claims 1 and 3, under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record and for reasons set forth below.

Applicant traverses the rejection (Response of 19 May 2008, page 4, last paragraph). The reason for the traversal is:

Applicants have provided several references which demonstrate that small molecule inhibitors of FGFR or methods screening for such inhibitors were known in the art at the time of the instant invention. Applicants assert that none of the references discloses FGFR-4 *per se* because it was not appreciated that FGFR-4 was a target for cancer therapy.

Applicant's arguments have been fully considered but have not been found persuasive for reasons of record and for reasons set forth below:

Adequate written description of the claimed genus, a method of treatment comprising administration of low molecular weight substances, must be found in the specification of the instant invention. As previously stated, none of the art cited by applicants overcomes the deficiencies in the specification as none discloses low molecular weight molecules as inhibitors of FGFR-4 signaling. Applicants assert that it was not appreciated that FGFR-4 was a target for cancer therapy. However, at the earliest priority date of the instant invention (22 January 1998) the following was known in the art:

Armstrong et al. teach FGFR-4 is expressed in leukemia cells and the high levels may represent aberrant expression induced by leukemogenesis (1992. Cancer Res 52:2004-2007, page 2006, 1st column, 2nd paragraph). McLeskey et al. (1994. Cancer Res. 54:523-530, abstract) teach that FGFR-4 is overexpressed in breast carcinoma cells and discuss the potential for designing therapeutic approaches to cancer involving manipulation of growth factor responses (page 529, 2nd column, last paragraph). Johnston et al. (Biochem J. 306:609-616) teach that FGFR-4 is involved in membrane ruffling in breast cancer cells (abstract) and this response may affect metastatic behavior of cancer cells (page 615, 2nd column, last paragraph). Thus, the art of record teaches the possible involvement of FGFR-4 in tumor growth and metastasis, but art cited by applicants does not disclose any low molecular weight molecules as inhibitors of FGFR-4 signaling.

Therefore, the rejection is maintained.

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35 U.S.C. § 103:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 4 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston et al (1995. Biochem J. 306:609-616). Johnston et al teach expression of FGFR-1, 3 and 4 in breast cancer cell lines (page 609, 2nd column 1st paragraph); the reference also teaches overexpression of FGFR-4 in primary breast tumor cells and teach that this receptor may have a role in breast tumorigenesis (page 609, 2nd column 1st paragraph). FGF (both acidic and basic), the ligand for FGFR, induces membrane ruffling in metastatic breast cancer cell lines, but not normal breast cells (page 609, 2nd column 2nd paragraph); "membrane ruffling is associated with cell motility and therefore could be important in determining the metastatic potential of cells" (page 614, 2nd column, 1st paragraph). The reference thus teaches the importance of stimulation of FGFR-4 in breast cancer tumorigenesis and metastasis. Johnston et al teach that FGF-induced cell growth and membrane ruffling was inhibited by expression of truncated FGFR-3 receptor in the test cells (page 613, 1st and 2nd column); the truncated receptor comprises the extracellular domain and the transmembrane domain but lacks the kinase

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domain and is thus a kinase inactive mutant. Thus, the reference teaches that a kinase inactive receptor, a kinase inactive FGFR-3 receptor, inhibits FGF-induced cell growth and membrane ruffling.

The Johnston et al reference does not teach a method of treatment of a carcinoma in a mammal wherein the mammal comprises a mutated FGFR-4 protein comprising administration of a kinase inactive FGFR-4.

However, it would be obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of Johnston et al, which teaches inhibition of FGF-induced breast cancer cell growth and membrane ruffling *in vitro* by administration of a truncated, kinase inactive FGFR-3 receptor and administer a kinase inactive FGFR-4 to treat carcinoma in a mammal, wherein the mammal comprises a mutated FGFR-4 protein. One of ordinary skill in the art would have been motivated to make the modification and would have anticipated success, because the art teaches FGFR-4 is known to be associated with breast cancer cells and administration of kinase inactive FGFR-3 receptor inhibits FGF-induced breast cancer cell growth and membrane ruffling. Additionally, Johnston et al teaches the FGFR-4 receptor is the one responsible for transducing the membrane ruffling response (page 614, 1st column, 2nd paragraph) and this ruffling response may affect metastatic behavior of cells (page 615, 2nd column, last paragraph). Furthermore, one of ordinary skill in the art, aware that cancer metastasis is predictive of poor prognosis, would be motivated to treat a patient with a method shown to be effective in inhibiting a cell response correlated with cell motility and metastasis.

Conclusion:

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is

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(571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. H. S./
Examiner, Art Unit 1647

/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647